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Breast and lung cancer are associated with a decrease in blood cell amino acid content

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Abstract

The description of different plasma amino acid profiles for specific types of cancer suggests that the metabolic alterations brought about by each type of tumor determine their own, distinctive profile of plasma amino acids. However, the blood cell pool represents an important percentage of the total amount of amino acids and has been reported to undergo significant changes in several physiological situations, thus raising the question of what effect a situation like cancer could have on amino acid blood compartmentation. We determined the levels of individual amino acids in blood, plasma and blood cell compartment of 14 lung cancer patients, 16 breast cancer patients and the corresponding healthy controls (n = 14 and 18, respectively). Cancer, a situation of increased amino acid demand, was accompanied by a decrease in the amino acid availability, of which the blood cell pool would be the main contributor. Thus, the fact that the blood cell pool reflects more intensely than plasma the changes in amino acid availability and undergoes changes according to the demand of amino acids, reinforces the important role of the cell pool in blood amino acid compartmentation and handling. The profiles of blood amino acids characteristic of different types of tumors that have been proposed by some authors could be extended to other compartments—in addition to the plasma—and even be more informative.

Keywords: Amino acids; Blood cells; Human; Cancer

1. Introduction

The presence of the tumor is associated with an alteration of the protein metabolism of the host that is mediated by the tumor itself and characterized by an increased whole body protein turnover [1,2]. As regards muscle protein metabolism, it is not clear whether increased proteolysis or reduced protein synthesis is the primary event in the muscle wasting associated with cancer [3]. The effects may be mediated by cytokines and tumor factors as well as by anorexia [4,5]. Moreover, the hypoglycemia of the host would suppose an important reduction of the energy available that would contribute to a decrease in protein synthesis [6,7].

Levels of plasma amino acids represent the net effect of all the factors influencing the total flux of amino acids in the body [8]. In fact, there have been reports focused on the role of the plasma amino acid profile as a marker of cancer-linked protein metabolism alterations [9–12]. The description of different plasma amino acid profiles for specific types of cancer, such as the small cell lung cancer [13] and the hepatocellullar carcinoma in patients with cirrhosis [9] suggests that the metabolic alterations of each type of tumor determine their own, distinctive profile of plasma amino acids. The possibility that some cancers can induce characteristic plasma free amino acid profiles suggests a role of these in the diagnosis and explanation of the origin of these diseases [11,14]. However, although at first plasma amino acids were considered the only ones involved in interorgan exchange, the blood cell pool represents an important percentage of the total amount of amino acids and has been reported to undergo significant changes in several physiological situations both in rodents and humans [15,16]. These findings pointed to a relationship between amino acid availability and blood compartmentation and raised the question of what effect a situation like cancer could have, given the lower availability of nutrients caused by the tumor. Two

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Table 1
Age, BMI, stage of the tumour, and weight loss presence in the patients included in the study

Lung cancer patients					Breast cancer patients				
Patient	Age	BMI	Stage	Weight loss	Patient	Age	BMI	Stage	Weight loss
1	71	23	III	Yes	1	65	25.9	IV	—
2	67	18.6	IV	Yes	2	69	19.9	III	Yes
3	72	26.2	IV	Yes	3	73	22.3	IV	Yes
4	59	22.9	IV	Yes	4	52	26.0	IV	—
5	53	26.5	IV	—	5	68	30.1	III	No
6	63	30.1	III	No	6	50	28.6	IV	—
7	58	26.5	III_B	No	7	58	28.1	II_B	No
8	63	23.1	IV	Yes	8	58	29.2	II	No
9	58	21.5	III	No	9	58	29.4	II	Yes
10	71	26.4	III	No	10	68	23.9	I	No
11	63	30.8	II	No	11	53	25.1	IV	Yes
12	64	18.6	III	Yes	12	67	29.5	—	—
13	73	24.7	II	No	13	34	24.5	II	No
14	67	18.8	IV	Yes	14	57	24.6	II	No
					15	59	26.7	III	No
					16	—	32.9	I	No

types of cancers were chosen: lung cancer in men and breast cancer in women, both of which have a very different degree of malignity, thus allowing us to have a wider vision of the effects cancer has on amino acid blood compartmentation.

2. Methods and materials

2.1. Subjects and sampling

Consistent with current guidelines in Spain, human blood samples were obtained from consenting lung and breast cancer patients (n = 14 and 16 respectively) and healthy subjects of both sexes (n = 14 and 18 respectively) who were undergoing a routine blood test. The age, BMI, stage of cancer, and weight loss presence for each cancer patient are shown in Table 1. After overnight fasting, 5 ml blood samples were obtained by venipuncture from the forearm, were kept in heparinized glass tubes at 4°C, and processed in the following 2 h.

2.2. Blood fraction amino acid analysis

Blood amino acid pool evaluation was carried out following a previously developed protocol [17]. In brief, two blood fractions were studied: plasma—obtained by centrifuging an aliquot of whole blood—and hemolysed whole blood—obtained by diluting (1:1) an aliquot of whole blood with the internal standard solution—L-methionine sulfone (Sigma, St. Louis, MO USA) 400 μM. The plasma was also diluted 1:1 with the internal standard solution and subsequently all blood fraction samples were deproteinized with cold acetone [18]. The clear supernatants were used for individual amino acid analysis using the Pico-Tag™ method [19] (Waters, Milford, MA USA) by separating the phenylthiocarbamyl amino acids obtained after derivatization with phenyl-isothiocyanate by means of HPLC (Waters) using a Pico-Tag™ column for free amino acids (Waters). Amino acid levels were calculated from the peak areas using the Maxima™ 820 program (Waters).

The plasma levels of amino acids (P), expressed as μM in plasma, and the amino acids in hemolysed whole blood (HWB), expressed as μM in whole blood were obtained from both fractions. The packed cell volume value for each sample—apparent hematocrit value—was determined after centrifugation at 15,000 g for 5 min; plasma trapped in blood cell fractions was estimated [20], and the amino acid values in the cell fractions corrected accordingly—true hematocrit value (Ht). Thus, the concentration of amino acids in both fractions referred to whole blood volume was calculated in the following way:

$$Pc = P(1\text{-}Ht/100)$$ Pc: amino acids in plasma (μM in whole blood)

$$Cc = HWB\text{-}Pc$$ Cc: amino acids in cells (μM in whole blood)

Although tyrosine is not strictly an essential amino acid (it can be synthesized from phenylalanine), it has been included in this group since its metabolic needs are above the levels of its precursor.

2.3. Statistics

Student's t-test and oneway ANOVA were performed to assess differences between cancer patients and healthy subjects within each sex group and to determine the effects of the stage and the type of tumor respectively. All statistics

Table 2
Anthropometrical data of the subjects included in the study. Values are mean ± SEM of 14 healthy men and 14 lung cancer patients and of 18 healthy women and 16 breast cancer patients respectively.

	Healthy subjects	Lung cancer patients	Healthy subjects	Breast cancer patients
Age, y	59.8 ± 2.1	64.4 ± 1.6	57.9 ± 2.4	59.3 ± 2.5
Weight, kg	75.6 ± 3.1	64.1 ± 3.5*	65.7 ± 2.2	64.6 ± 2.0
Height, m	1.67 ± 0.02	1.63 ± 0.02	1.55 ± 0.02	1.56 ± 0.01
BMI, kg/m^2	26.9 ± 0.6	24.1 ± 1.1*	27.3 ± 0.84	26.7 ± 0.83
Haematocrit, %	44.7 ± 1.4	37.8 ± 1.5*	41.1 ± 0.57	34.8 ± 1.1*

* $P < 0.05$ control *vs* cancer.

were performed with DBASE IV and SPSS-WIN packages for PC.

3. Results

Table 2 shows the anthropometrical features of each group. Lung cancer patients had a lower weight, BMI and true hematocrit values than healthy men, whereas women with breast cancer only had lower values of true hematocrit than healthy women. The rest of the parameters were not significantly different between cancer and healthy groups.

Table 3 shows that lung cancer patients had a lower concentration of essential amino acids in blood than healthy men, although only valine and the essential amino acids as a whole reached statistically significant values. With regards to the non essential amino acids, blood concentration of proline was significantly lower in cancer patients, whereas mean value of the sum of non essential amino acids was not different between both groups. Total blood amino acid concentration was statistically lower in cancer patients compared to the control group. There were no differences between lung cancer patients and healthy subjects in essential and non essential amino acid plasma contributions, either individual or as a whole, except in the case of ornithine, which was higher in cancer patients. Nevertheless, there were changes in the cell contribution values of isoleucine, leucine, valine, tyrosine and threonine and total essential amino acids, which were inferior in cancer patients, as well as in the cell contribution of glutamine, aspartate, serine, proline, sum of non essential and sum of total amino acids, which were also lower.

Table 4 shows the blood, plasma and cell levels of amino acids in healthy women and women with breast cancer.

Table 3
Blood, plasma and cell levels of amino acids in healthy men and women with lung cancer. Results are expressed per blood unit volume (μM). Values are mean ± SEM of 14 men in each group.

	Blood		Plasma		Cells	
	Control	Lung Control	Control	Lung control	Control	Lung cancer
Isoleucine	55.1 ± 4.5	48.2 ± 2.6	36.1 ± 2.6	35.3 ± 1.7	19.1 ± 2.2	12.9 ± 1.4*
Leucine	133 ± 6.9	115 ± 6.0	87.6 ± 4.5	83.5 ± 4.8	45.2 ± 3.8	31.7 ± 2.9*
Valine	227 ± 13	191 ± 9.6*	152 ± 7.7	140 ± 8.0	75.8 ± 7.3	50.9 ± 5.1*
Histidine	56.4 ± 3.7	49.3 ± 2.3	38.4 ± 1.7	34.7 ± 2.0	18.0 ± 2.8	14.6 ± 1.4
Lysine	91.0 ± 5.4	81.5 ± 5.6	83.1 ± 5.5	78.2 ± 7.3	7.9 ± 2.7	3.3 ± 5.0
Phenylalanine	52.4 ± 2.2	54.9 ± 4.1	35.4 ± 1.4	40.3 ± 3.8	16.9 ± 1.4	14.7 ± 1.8
Tyrosine	71.5 ± 3.1	65.3 ± 2.7	43.2 ± 2.0	45.3 ± 2.9	28.3 ± 2.0	20.0 ± 1.5*
Threonine	117 ± 9	95.3 ± 7.5	74.7 ± 4.7	68.8 ± 5.5	42.4 ± 4.6	26.5 ± 2.7*
Methionine	20.8 ± 0.9	20.8 ± 1.5	14.8 ± 0.7	16.1 ± 1.0	5.9 ± 0.5	4.7 ± 1.0
ESSENTIAL	827 ± 40	721 ± 24*	566 ± 24	542 ± 24	261 ± 24	179 ± 18*
Glutamine	567 ± 18	514 ± 26	360 ± 12	355 ± 19	208 ± 10	159 ± 13*
Glutamate	203 ± 15	208 ± 11	37.1 ± 4.9	39.7 ± 3.5	166 ± 12	168 ± 9.9
Asparagine	76.9 ± 9.1	79.9 ± 7.2	24.0 ± 3.6	31.6 ± 4.2	52.9 ± 6.0	48.3 ± 5.3
Aspartate	129 ± 16	87.0 ± 13	5.8 ± 0.9	8.6 ± 4.2	12 ± 16	78.5 ± 14*
Glycine	256 ± 11	251 ± 12	120 ± 7	133 ± 12	136 ± 6.5	118 ± 8.4
Serine	116 ± 7	107 ± 7	60.8 ± 3.2	68.1 ± 6.6	55.5 ± 6.0	38.7 ± 4.6*
Alanine	369 ± 21	321 ± 19	231 ± 12	213 ± 16	137 ± 12	108 ± 14
Proline	180 ± 12	136 ± 17*	121 ± 9	99.3 ± 12	58.5 ± 5.5	36.8 ± 6.1*
Hydroxyproline	17.5 ± 2.1	16.3 ± 1.9	11.0 ± 1.4	11.8 ± 1.3	6.5 ± 0.9	4.5 ± 1.0
Ornithine	65.3 ± 5.7	71.2 ± 4.5	32.3 ± 2.7	45.4 ± 3.8*	33.0 ± 5.5	25.8 ± 3.3
NON ESSENTIAL	1991 ± 67	1803 ± 80	1009 ± 28	1009 ± 53	982 ± 54	794 ± 52*
TOTAL	2854 ± 100	2536 ± 81*	1591 ± 48	1570 ± 60	1263 ± 80	967 ± 64*

* $P < 0.05$ control *vs* lung cancer.

Table 4
Blood, plasma and cell levels of amino acids in healthy women and women with breast cancer. Results are expressed per blood unit volume (μM). Values are mean ± SEM of 18 y 16 women in each group.

	Blood		Plasma		Cells	
	Control	Breast cancer	Control	Breast cancer	Control	Breast cancer
Isoleucine	48.8 ± 4.2	40.1 ± 2.8	32.5 ± 2.4	30.6 ± 1.9	16.3 ± 1.9	9.50 ± 1.2*
Leucine	115 ± 6.5	109 ± 9.2	77.4 ± 3.9	77.5 ± 3.5	37.5 ± 3.3	31.1 ± 8.3
Valine	230 ± 15	182 ± 12*	150 ± 7.9	139 ± 8.5	80.1 ± 7.6	43.6 ± 4.7*
Histidine	54.1 ± 2.7	52.8 ± 2.8	37.9 ± 1.7	39.4 ± 2.1	16.2 ± 2.3	13.4 ± 1.8
Lysine	105 ± 8.4	101 ± 8.2	90.9 ± 4.5	94.6 ± 6.1	14.5 ± 5.5	6.43 ± 6.7
Phenylalanine	51.4 ± 1.9	50.0 ± 1.7	5.4 ± 1.2	38.5 ± 1.8	16.0 ± 1.7	11.5 ± 0.68*
Tyrosine	72.8 ± 4.3	63.2 ± 4.0	44.4 ± 2.3	43.5 ± 2.4	28.4 ± 2.2	19.6 ± 1.8*
Threonine	118 ± 8.3	106 ± 4.2	75.1 ± 4.9	76.1 ± 3.3	43.3 ± 3.6	29.6 ± 2.8*
Methionine	20.3 ± 1.2	21.4 ± 1.5	14.7 ± 0.86	14.9 ± 0.97	5.52 ± 0.05	6.51 ± 1.1
ESSENTIAL	816 ± 41	725 ± 31	558 ± 22	554 ± 22	238 ± 22	174 ± 16*
Glutamine	525 ± 17	580 ± 29	344 ± 11	398 ± 19*	181 ± 9.0	182 ± 14
Glutamate	223 ± 15	176 ± 14*	33.5 ± 2.4	34.2 ± 4.3	189 ± 13	141 ± 13*
Asparagine	52.5 ± 6.7	74.6 ± 7.1*	18.1 ± 2.9	27.8 ± 3.0*	34.4 ± 4.2	46.8 ± 4.6
Aspartate	116 ± 9.7	108 ± 8.5	7.15 ± 0.85	3.20 ± 0.27*	109 ± 9.4	104 ± 8.5
Glycine	270 ± 12	240 ± 16	129 ± 8.3	121 ± 9.3	142 ± 6.4	118 ± 9.4*
Serine	115 ± 4.3	107 ± 5.3	61.8 ± 2.6	62.4 ± 2.3	53.0 ± 2.4	44.2 ± 4.2
Alanine	400 ± 23	345 ± 29	249 ± 14	231 ± 19	151 ± 11	112 ± 12*
Proline	185 ± 10	173 ± 12	122 ± 6.0	130 ± 7.6	63.3 ± 5.6	43.1 ± 5.3*
Hydroxyproline	13.7 ± 1.4	17.7 ± 1.6	8.87 ± 0.77	12.0 ± 1.2*	4.87 ± 0.70	6.14 ± 0.73
Ornithine	72.1 ± 5.1	63.3 ± 4.4	33.5 ± 2.3	35.7 ± 2.6	38.6 ± 4.5	27.5 ± 3.5
NON ESSENTIAL	1972 ± 54	1871 ± 74	1006 ± 32	1046 ± 36	915 ± 29	859 ± 42*
TOTAL	2788 ± 84	2599 ± 92	1564 ± 45	1600 ± 47	1153 ± 46	1036 ± 55*

* $P < 0.05$ control *vs* breast cancer.

Amino acid blood concentration values, individual and as a whole, were similar between breast cancer patients and healthy women except in the case of valine and glutamate, which were lower in cancer patients, and asparagine, which was higher. There were no differences in plasma contribution values either of individual amino acids or of their sum, except in the case of glutamine, asparagine and hydroxyproline, which were higher in breast cancer patients, and aspartate, which was lower. As regards to the blood cell pool, cell contributions of isoleucine, valine, phenylalanine, tyrosine and threonine, among the essentials, and glutamate, glycine, alanine and proline, among the non essentials, were lower in women with breast cancer, and so were the sum of essential, non essential and total amino acids.

4. Discussion

Lung cancer involved a reduction in the availability of blood amino acids which would be due both to the malnutrition associated to tumor bearing state [10] and to an increase of the amino acid demand as a consequence of the presence of the tumor, since the circulating pool is its main nitrogen source [21].

To face their growth, tumors require essential amino acids and others such as glutamine, glycine and aspartate—for purine and pirimidine synthesis—and serine—for membrane lipid component synthesis—thus bringing about a selective demand of amino acids [7] leading to a gradual loss of muscle mass to face the protein turnover in tissues [7,22] which results in a lower availability of amino acids, especially essential ones. Blood levels of branched-chain amino acids (BCAAs) were significantly lower in lung cancer patients compared to healthy subjects (415 *vs* 354 μM, $p = 0.034$) whereas in the case of breast cancer, differences did not reach statistical significance (394 *vs* 331 μM, $p = 0.057$), which agrees with a different degree of severity in the alterations in the host protein metabolism induced by both types of neoplasia. Breast cancer affected the amino acid availability to a lesser extent in comparison with the effect of lung cancer, as reflected by the sum of total amino acids: 7% decrease in breast cancer patients—compared to healthy controls—versus 11% decrease in lung cancer patients (see Fig. 1). This lower intensity of changes in blood amino acid levels would reflect either a capacity to resist the effect of the tumor on the part of the host, or a lower capacity of breast cancer to bring about metabolic stress compared to lung cancer. The latter is worth considering since only 33% of breast cancer patients underwent weight losses during the development of the disease as opposed to the 54% observed in the group of lung cancer patients (Table 1). Moreover, our results show that changes in the amino acid blood compartmentation associated to cancer appear to be more influenced by its degree of severity, i.e. its spread (stage), than by the organ site in which it developed. Thus, oneway ANOVA revealed a significant effect of the stage of tumor on blood amino acid concentrations and cell and plasma contributions for essential, non essential

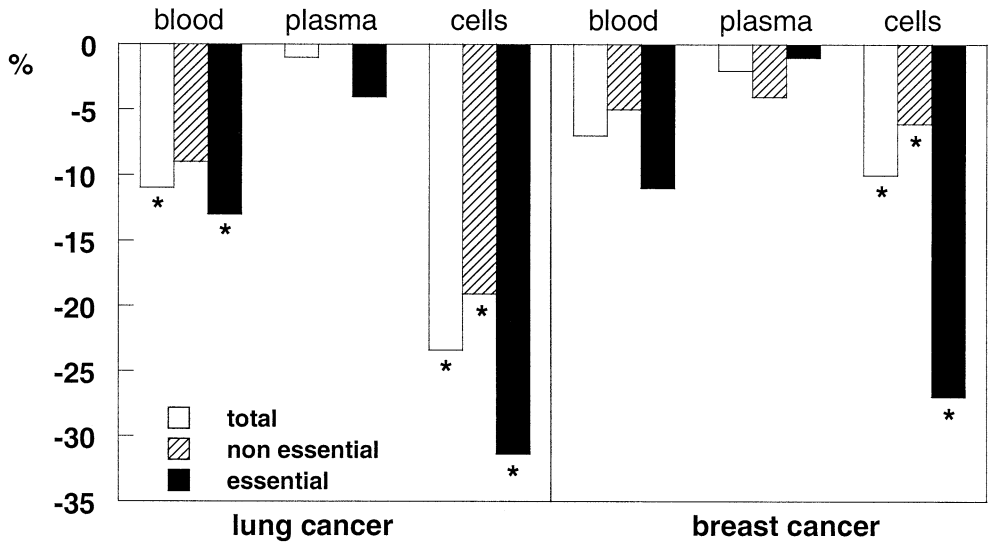

Fig. 1. Percentage variation in the essential, non essential and total amino acid blood concentration and plasma and blood cell contributions in lung and breast cancer patients with respect to corresponding healthy subjects. *$P < 0.05$ cancer *vs* healthy subjects.

and total amino acids. When the type of tumor was included in the statistical analysis as a covariate, no significant effect was found, whereas the stage effect kept its significance. In fact, breast cancer usually does not present such a fast growth neither it is so aggressive for the host as lung cancer, which is metabolically very active [23], causing high metabolic stress to the host who often ends in cachexia [6,24]. Moreover, the degradation of proteins would not be so intense in breast cancer patients—compared to lung cancer patients—given their greater fuel availability due to the larger proportion of fat mass suggested by their respective BMI values (see Table 2). Values of plasma free fatty acids three times higher to those of healthy women have been described in these same breast cancer patients [25].

The cancer-related differences in BMI values in both genders could also be indicative of a deficient nutritional status in lung cancer patients due to a lower food intake, which could be related to the amino acid alterations found in these patients. However, since food intake in these patients was not controlled, this extreme cannot be confirmed.

In both types of cancers, the amino acid plasma pool as a whole did not substantially modify its contribution to the blood pool, in spite of the increase of the ratio of plasma to cells due to the 15% decrease in the hematocrit values associated to the presence of the tumor in both cases. The reduction of the hematocrit constitutes an alteration common in cancer patients and its development can be affected by multiple factors such as a reduction of the production of erythrocytes and their survival, secretion of hemolytic factors by the tumor, host malnutrition, etc. [26]. The decrease in the hematocrit value in lung cancer patients is accompanied with a 15% reduction of the plasma concentration (i.e. μM in plasma) of the essential amino acids and a 11% in the cases of non essential amino acids (data not shown). This decrease represents 10% and 5%, respectively, in breast cancer patients, which agrees with the previously reported idea of breast cancer patient plasma amino acid profile as the most similar profile to healthy women between different types of cancer [14].

Although cancer-associated hematocrit decrease was involved in the lower values of the cellular contribution of amino acids, the cell concentration (i.e. μM in cells; data not shown) was still lower in cancer patients, especially in the case of the essential amino acids. Thus, essential amino acid cell contribution decreased 31% in lung cancer patients and 27% in breast cancer patients, whereas the corresponding concentrations decreased 19% and 22% respectively. Consequently, the effect of both lung and breast cancer on amino acid availability was actually higher in the blood cell pool, than in the plasma pool as reported above. Thus, the cancer-linked increase in amino acid demand would cause a reduction in the availability of amino acids, of which the cell pool would be the main contributor.

In this study a situation of greater amino acid demand as a consequence of the presence of the tumor is accompanied by alterations in the amino acid availability that are mainly due to variations in the blood cell pool (see Fig. 1). Thus, the fact that the blood cell pool reflects more intensely than plasma the changes in amino acid availability, and undergoes changes according to the demand of amino acids by the organism, reinforces the important role of the cell pool in blood amino acid compartmentation and handling previously suggested [16]. As far as we know, this is the first report on amino acid blood compartmentation in cancer patients, and leads to the conclusion that the profiles of blood amino acids characteristic of different types of tumors proposed by some authors [27], could be extended to other compartments, in addition to the plasma, and as such be more informative.

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